## REMARKS

The title, abstract, and priority claim have been amended as requested by the Examiner. Claim 1 has been amended to clarify the language defining the $R_1$ substituent. Claim 1 has also been amended to specify that $R_{14}$ and $R_{15}$ are not both simultaneously hydrogen. Similarly, Claim 9 has been amended to specify that $R_{14}$ and $R_{15}$ are not both simultaneously hydrogen. Non-elected Claims 10-20 have been cancelled without prejudice to pursuing these claims in continuation, divisional, or continuation-in-part applications. New Claims 21-28 have been added. Independent Claim 21 recites compounds in which $R_{14}$ and $R_{15}$ are both simultaneously hydrogen. Dependent Claims 22-28 depend from Claim 21. Thus, compounds within the scope of original Claims 1-9 fall within the scope of amended Claims 1-9 or newly added Claims 21-28. Claims 1-9 and 21-28 are now pending in the application.

Applicants have carefully considered all of the Examiners rejections and comments but respectfully submit that the claims are allowable for at least the reasons presented below.

Rejections Under § 102

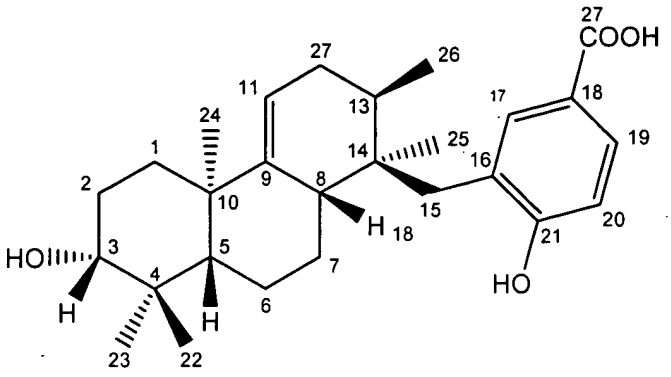
The Examiner has rejected Claims 1-9 under 35 U.S.C. § 102(a) as being anticipated by Suh et al. (U.S. Patent No. 6,593,363). The Applicants note that with an issue date of July 15, 2003, Suh is not properly § 102(a) art, nor is it properly § 102(e) art. Applicants do, however, recognize that PCT Publication No. WO99/37600 published on July 29, 1999. Applicants comments address this publication, which will be referred to as the Suh-PCT.

The Suh-PCT discloses various diterpene derivatives. Each specific diterpene derivative disclosed by Suh-PCT as well as the general class of diterpenes disclosed contain hydrogen atoms corresponding to the $R_{14}$ and $R_{15}$ substituents in the instant claims. The Applicants note that pending Claims 1-9 recite compounds in which $R_{14}$ and $R_{15}$ are not both hydrogen. Accordingly, pending Claims 1-9 are patentable over the Suh-PCT.

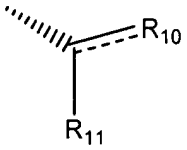
Claims 21-28 are directed to compounds in which $R_{14}$ and $R_{15}$ are both hydrogen. Applicants respectfully submit that, nonetheless, the compounds recited in Claims 21-28 are fully supported by the disclosure of U.S. Provisional Application 60/134,295, from which the instant application claims priority and which was filed on May 14, 1999. Accordingly, Suh-PCT is not available as prior art to Claims 21-28, which claim priority to at least May 14, 1999.

The fact that Applicants have focused on the $R_{14}$ and $R_{15}$ substituents in distinguishing Suh-PCT should not be interpreted as implying that there are not other novel features of the compounds of Claims 1-9 and 21-28 as compared to Suh-PCT.

The Examiner has also rejected Claims 1-3 and 6-9 under § 102(a) as being anticipated by Jaki et al. ("A Novel Extracellular Diterpenoid with Antibacterial Activity from the Cyanobacterium Nostoc commune," *J. Nat. Prods.*, 1999, 62, 502-503). Jaki discloses the following chemical structure:




Applicant respectfully submits that this compound does not fall within the literal scope of the pending claims. For example, carbon 13 of the Jaki structure contains a hydrogen substituent below of the plane of the molecule. In contrast, the instant claims recite the following substituent below the plane of the molecule on the carbon corresponding to carbon 13 of the Jaki structure:




Any hydrogen substituent in the claims on the corresponding carbon 13 position (e.g., $R_9$ = H) must be above of the plane of the molecule. Accordingly, Applicants respectfully assert that Jaki does not anticipate Claims 1-3 and 6-9, and request that the rejection based on Jaki be reconsidered and removed.

Rejections Based on The Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner rejected Claims 1-9 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over Claims 1-12 and 25-28 of U.S. Patent No. 6,365,768. Applicants, without addressing the merits of or otherwise acquiescing to this rejection, herewith submit a terminal disclaimer in compliance with 37 C.F.R. 1.321(b), and

disclaim the terminal portion of any patent granted on this application extending beyond the expiration date of co-owned U.S. Patent 6,365,768. Therefore, this rejection is obviated.

Rejections under § 112 – Enablement

The Examiner rejected Claims 1-9 under 35 U.S.C. § 112, ¶ 1 as failing to comply with the enablement requirement. The Examiner asserted that the disclosure in the specification of three compounds having efficacy was insufficient to enable the claims. In order to satisfy the enablement requirement, the specification must teach those of skill in the art how to make and use the invention without undue experimentation. *See* M.P.E.P. § 2164.01. The Applicants respectfully submit that the instant specification provides such a teaching.

The specification teaches how to make the claimed compounds by describing synthetic methods and schemes at, for example, page 30, line 6 to page 32, line 7; page 33, line 14 to page 38, line 15; page 39, line 22 to page 40, line 5; page 40, line 26 to page 56, line 28; and page 69, line 1 to page 72, line 19. The Applicants respectfully submit that those of skill in the art would be able to follow these methods to synthesize the full range of claimed compounds without undue experimentation.

As stated in the specification, there are many diseases and disease states that can be treated using "compounds that selectively influence the production of TNF-α and/or IL-1." Page 29, line 31 to page 30, line 1. The specification teaches those of skill in the art how to use the claimed compounds in this manner. For example, the specification states that

> [t]he selectivity of a candidate modulator can be established *in vitro* by testing the toxicity and effect of a candidate modulator on a plurality of cell lines that exhibit a variety of cellular pathways and sensitivities. The data obtained from these *in vitro* toxicity studies may be extended to animal models, including accepted animal model studies and human clinical trials, to determine toxicity, efficacy, and selectivity of the candidate modulators.

Page 57, lines 21-26. More specifically, the specification teaches that TNF-α and/or IL-1 activity can be determined by treating murine macrophage cells RAW 264.7 with the claimed compounds. *See* page 74, lines 7-16. The cells can then be stimulated with various agents such as lipopolysaccharide or heat-killed *Staph aureus*. *Id.* Supernatants may then be assayed for levels of TNF-α, IL-1, IL-6, IL-10, IL-18 or other cytokines by either ELISA or bioassay. *Id.* Thus, those of skill in the art can use this simple assay to determine TNF-α and/or IL-1 activity without undue experimentation.

The specification further teaches those of skill in the art how to use the claimed compounds in pharmaceutical compositions. For example, page 57, line 27 to page 66, line 14 describes pharmaceutical compositions, routes of administration, and dosages. Thus, those of skill in the art would be able to use the claimed compounds in pharmaceutical applications without undue experimentation.

The Examiner argues that three examples are insufficient to enable the claimed compounds. However, "[c]ompliance with the enablement requirement...does not turn on whether an example is disclosed." M.P.E.P. § 2164.02. "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue amount of experimentation." *Id.* "[L]ack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." *Id.* As discussed above, synthetic and assay methods are disclosed in the specification with sufficient detail to enable those of skill in the art to make and use the claimed compounds. No other disclosure is required. Results showing that a particular or representative number of the claimed compounds have a particular efficacy is not necessary to satisfy the enablement requirement. *See* M.P.E.P. § 2164.08(b) ("The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than is normally required in the art.").

Rejections under § 112 – Indefiniteness

The Examiner rejected Claims 1-9 under 35 U.S.C. § 112, ¶ 2 as being indefinite. The Examiner argued that Claim 1 did not positively recite what the compound may be. The Applicants have amended Claim 1 to specify what species the $R_1$ substituent is selected from with accompanying provisos. The Applicants respectfully submit that the present amendment addressed the Examiners rejection.

Objections to Title, Abstract, and Related Cases Section

The Examiner asserted that the title was not descriptive and that the abstract required revision. The Applicants have amended the title and abstract to address the Examiners concerns. The Examiner also requested that the status of related cases be updated in the specification. Accordingly, the Applicants have amended the priority claim.

References Cited in 09/570,202

The Examiner stated that the file of parent application 09/570,202 was incomplete and did not contain the references cited in the IDS submitted on July 11, 2002. Accordingly, the Applicants are submitting with this amendment a copy of the July 11, 2002 IDS with the references cited. The Applicants respectfully request that the Examiner consider these references and indicate his consideration.

## CONCLUSION

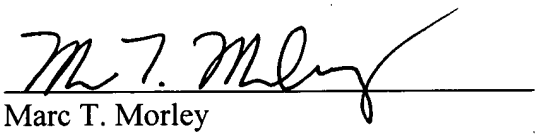
The Applicants respectfully submit that they have overcome the Examiner's rejections by the foregoing amendments and remarks and request a timely issuance of a Notice of Allowance.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 10/13/04

By: 

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